

# Transvesical NOTES: Survival Study in Porcine Model

Jasneet Singh Bhullar, MD, MS, Gokulakrishna Subhas, MD, MRCS, Aditya Gupta, MD, Michael J. Jacobs, MD, Melissa Decker, LVT, Boris Silberberg, MD, Vijay K. Mittal, MD

## ABSTRACT

**Background and Objectives:** The optimal access route and method for natural orifice transluminal endoscopic surgery (NOTES) has not been established. A transvesical approach, with its low rate of peritoneal contamination, is an effective clean portal of entry, but a safe urinary bladder closure has been a challenge. We developed a new technique for a safe, pure transvesical NOTES approach.

**Methods:** Four female piglets were used in the study. With the pigs under anesthesia, a flexible cystoscope (15Fr) was used to make an endoscopic cystotomy; diagnostic peritoneoscopy of the abdominal quadrants was done with biopsies and hemostasis. At the end, a Vicryl loop was pushed to close the bladder incision while the incision edges were pulled inwards. The pigs were euthanized after 2 wk, and necropsies were performed.

**Results:** No bowel injury was noted in any of the 4 pigs. Satisfactory bladder closure was done in 2 pigs, while a partial closure was achieved in 1 case. In the postoperative period, the pigs showed no signs of pain or distress, voided normally, and had a good appetite. On necropsy, we noted healed cystotomy incisions, no intraabdominal adhesions, and no adhesions at the site.

**Conclusion:** Our new technique for endoscopic cystotomy overcomes previously reported risks for bowel injuries. Using this route gives good spatial orientation and access to all quadrants, including the pelvis. Biopsies with good hemostasis can be easily achieved. Lack of intraperi-

toneal changes postoperatively indicate that this procedure may be safe for humans.

**Key Words:** NOTES, Transvesical, Porcine model, Transvesical NOTES, Peritoneoscopy.

## INTRODUCTION

Significant advances have been made towards the development of minimally invasive techniques, and surgeons continue to search for new methods to minimize the morbidity of surgery.<sup>1</sup> The endeavor towards minimizing skin incisions has been evident in all branches of surgery, including general surgery, orthopedics, urology, and especially branches requiring a high degree of precision, like cardiothoracic surgery. Endoscopic saphenous vein grafting for coronary artery bypass graft is now the norm rather than the exception, and we are seeing newer techniques such as minimally invasive valve repairs and replacements take hold. Urologists have been developing technology for noninvasive procedures for years.<sup>1</sup> For example, renal stones that were formerly extricated using open procedures are now approached in a minimally invasive manner, including use of shockwave lithotripsy, ureteroscopy, and percutaneous methods.

Desire for less invasive surgical procedures has led to the development of minimally invasive surgery. This concept was pioneered in 1985 by Eric Muir, who performed the first successful laparoscopic cholecystectomy. The concept of performing surgery through natural body orifices, though always fascinating, has only come to fruition recently, and is now becoming the norm. Natural orifice transluminal endoscopic surgery (NOTES) is still an evolving minimally invasive modality for performing abdominal and retroperitoneal surgery with no transcuteaneous abdominal incisions. The idea of scarless surgery is naturally appealing. NOTES eliminates the need for abdominal incisions, resulting in decreased pain, faster convalescence, improved cosmesis, and elimination of risk for surgical-site infections and hernias. This technique also lends its utility in performing procedures where conventional laparoscopic techniques would be a disadvantage, as in morbidly obese patients. However, it also

Department of Surgery, Providence Hospitals and Medical Centers, Southfield, MI, USA (Drs. Bhullar, Subhas, Gupta, Jacobs, Mittal); Department of Patient Care Research, Providence Hospitals and Medical Centers, Southfield, MI, USA (Dr. Silberberg, Ms. Decker).

We are thankful to Rebecca Walendzak of Cook Medical Devices, Kathleen Paul of Covidien and Adam Krause of Karl Storz Endoscope for helping us with the equipment needed for the study.

Address correspondence to: Jasneet Singh Bhullar, MD, MS, Department of Surgery, Providence Hospital and Medical Centers, 16001 West Nine Mile Road, Southfield, MI 48075, USA. Telephone: (248) 849-7638, Fax: (248) 849-5380, E-mail: drjsbhullar@gmail.com.

DOI: 10.4293/108680812X13517013317950

© 2012 by JSLS, *Journal of the Society of Laparoendoscopic Surgeons*. Published by the Society of Laparoendoscopic Surgeons, Inc.

shares the potential for many complications associated with laparoscopic surgery: difficulties with poor visibility, maneuverability, and organ grasping are likely to be increased as distances are further and the equipment needed is likely to be more specialized.<sup>2</sup> Other problems are associated with NOTES, the biggest being the risk of contamination in performing a relatively sterile procedure through a contaminated portal (i.e., the gastrointestinal or the genitourinary tract), and the problem of successful subsequent closure of the viscerotomy wound.

Numerous studies have been conducted in the field of NOTES, using different access routes. Gettman and colleagues described a transvaginal nephrectomy in a porcine model in 2002, which was the first experimental application of natural orifice surgery.<sup>1</sup> Since then, others have reported the use of the gastrointestinal tract as a portal for cholecystectomy, gastrojejunostomy, appendectomy, splenectomy, tubal ligation, and other procedures. Many successful procedures like cholecystectomy have been reported in humans via the transvaginal route. Interest arose regarding the bladder as a portal first in 2006, with Lima and colleagues reporting on transvesical peritoneoscopy in porcine models in 2006.<sup>3</sup> Metzelder et al.<sup>4</sup> used a transurethral/transvesical approach with the assistance of an umbilically placed “two in one system,” including a 0-degree optic and a 5-degree working channel. They were able to successfully perform nephroureterectomy and bilateral tubo-ovariectomy in piglets using this setup. At the end of this procedure, they investigated several techniques for bladder closure and determined that bladder closure with an Endoloop was a feasible option when done through the peritoneum. This was a significant finding, as the transvesical route has less potential for contamination compared with the transgastric and the transanal routes.<sup>5</sup> Therefore, we chose the transurethral/transvesical route as the access point for our study.

One advantage of NOTES compared with open or laparoscopic surgery in the urologic setting is the complete avoidance of abdominal or flank incisions.<sup>1</sup> Pain is a common sequela after surgery, with surgical trauma stimulating painful impulses via nociceptors. Theoretically, decreased postoperative pain due to a smaller incision would result in faster convalescence, decreased use of narcotics and their antecedent side effects, and shorter hospitalizations. Avoiding large abdominal and flank incisions also eliminates the potential for both short-term and long-term complications, the most notable being surgical-site infections and incisional hernias.

The 3 available portals for NOTES are the gastrointestinal tract (includes transoral and transanal routes), the urinary tract, and the transvaginal route in females. At present, gastric

and intestinal closures are technically difficult, partly because of the wall thickness, which is more so in the case of the stomach. Further, a risk of intraperitoneal contamination and infection results from exposure to gastric, intestinal, or distal colonic contents. The urinary tract is normally sterile, and the transvesical approach minimizes the chances of intraperitoneal or retroperitoneal contamination.<sup>1,5,6</sup>

In addition to being potentially safer from an infectious point of view, transvesical NOTES has some additional inherent advantages compared with the transgastric and transanal routes. It allows for visualization of all intraperitoneal structures within a direct line of sight.<sup>1</sup> A major limitation of gastric access is an inability to maintain spatial orientation. All instruments pass through working channels on the endoscope, with the light source and camera in line. During transgastric NOTES, some maneuvers require working off-axis, which further increases the difficulty of complex procedures. The transvesical approach allows for visualization of all intraperitoneal structures within a direct line of sight. Using the bladder as a portal of entry also affords the flexibility of using rigid or flexible instruments. Also, accessing the peritoneum transvesically moves the operating field away from the airway, simultaneously creating a familiar and comfortable environment for the anesthesiologist and the surgeon alike.

Limitations to using the transvesical approach exist as well; the most significant is the small diameter of the urethra, which limits the caliber of instruments that can be introduced through this route. Moreover, the length of the urethra in male patients can be a limiting factor, making this procedure decidedly easier in females. Nonetheless, the issue of urethral length has been overcome with ureteroscopy, and should not represent a significant challenge for transvesical NOTES.

### **The Aims of Our Study Were:**

1. To evaluate our new technique of accessing the peritoneum transvesically, by opening the bladder in layers under vision, thus overcoming the risk of visceral organ injury mentioned in previously reported techniques.
2. To evaluate the practicality and results of closing the cystotomy transurethrally using a Vicryl loop.
3. To evaluate the effects of transvesical peritoneal access on bladder healing, both grossly and histopathologically.
4. Because most of the reported transvesical NOTES animal studies have been done as feasibility studies only, we planned our study in a survival porcine model to accurately evaluate the effects and results of the procedure.

## MATERIALS AND METHODS

Four female piglets, each weighing between 30lb to 35lb (14 kg to 16 kg), were used for the experiment. The animals, under general anesthesia, were prepped and draped using standard sterile precautions, as for a cystoscopy. They were secured on the operating table in a supine position, so as to enable the change of the table position for subsequent surgery. The main instruments used for our study purposes included a Karl Storz flexible cystoscope (15Fr with 7Fr working channel), a flexible grasper, and bug-bee electrode.

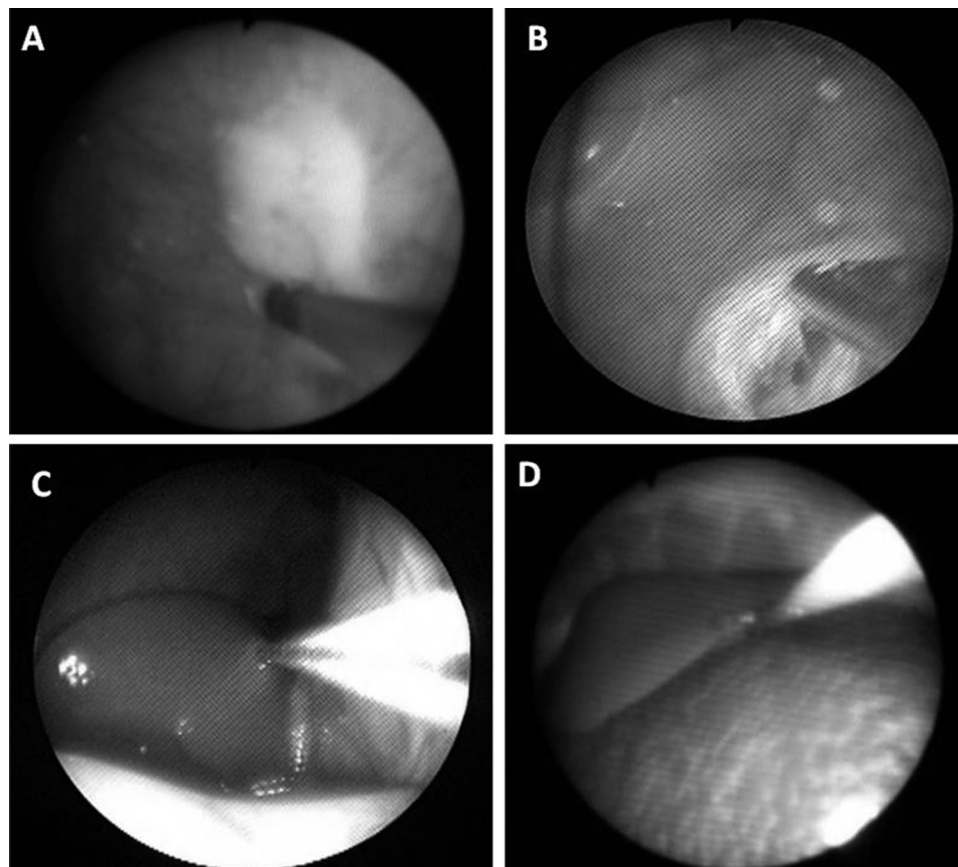
The flexible cystoscope was introduced per urethra, and the urinary bladder was entered and inspected. The bladder was then emptied and 100ml of glycine solution was infused. The glycine solution enabled the diathermy to work inside the bladder. An area on the postero-superior aspect was selected. At this location, a 0.5-cm vertical area was diathermized in a gradual manner, using a bug-bee electrode (**Figure 1A**). After the diathermy was complete,

a cup biopsy forceps was used to open the diathermized area in layers, so as to enter the peritoneum under direct vision (**Figure 1B**). Initial diathermy of the superficial layers of the bladder wall kept the vision clear as no bleeding was noted when the cystotomy was being made.

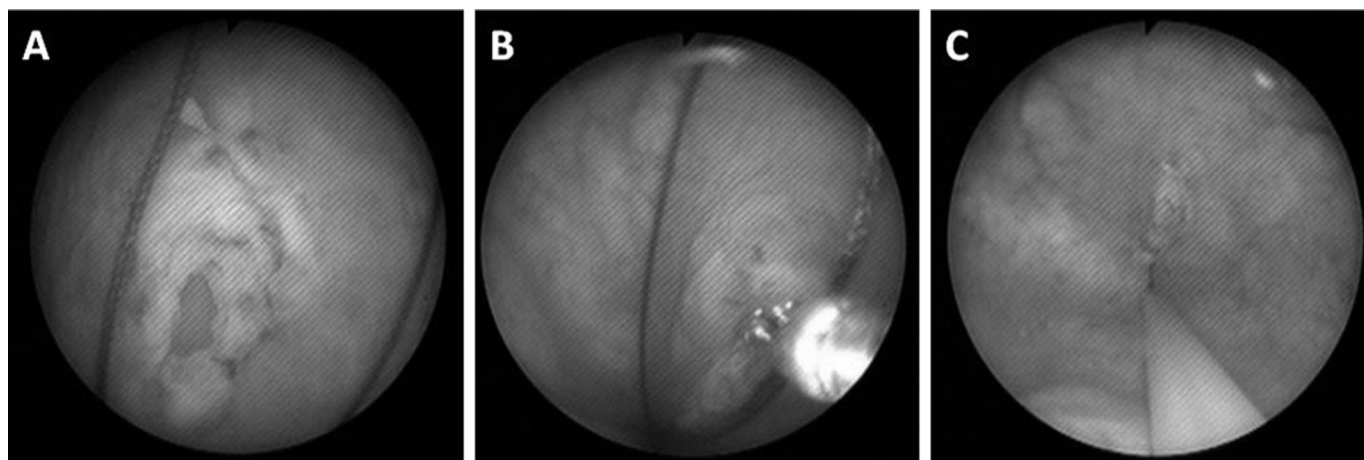
The cystoscope was introduced into the peritoneal cavity through the cystotomy, and a pneumoperitoneum was created. The cystotomy fitted snugly around the cystoscope, thus avoiding any spillage of bladder contents intraperitoneally. Diagnostic peritoneoscopy was done to inspect all 4 abdominal quadrants. Biopsies were taken from the liver, spleen, and omentum (**Figure 1C**). Adequate hemostasis was achieved using the bug-bee electrode (**Figure 1D**).

### Bladder Closure

Subsequent to obtaining biopsies and ensuring hemostasis, the pneumoperitoneum was evacuated. The instruments were pulled back in the bladder under direct vision,



**Figure 1.** **A.** Diathermy of the bladder wall. **1B.** Opening bladder in layer. **1C.** Liver biopsy. **1D.** Biopsy site diathermy.



**Figure 2.** **A.** Vicryl loop in position around cystotomy site. **2B.** Loop closure of the opening. **2C.** Closed bladder opening.

and lastly the cystoscope was withdrawn. A 1-0 Vicryl loop was pushed in the bladder along the side of the cystoscope. It was positioned so as to encircle the cystotomy (**Figure 2A**). Once the loop was in position, the edges of the incision were grasped using the flexible grasper. The loop was pushed to close the bladder, while pulling the incision edges inwards with the grasper. In this manner, the loop was tightened and a secure bladder closure was achieved (**Figures 2B & 2C**). After achieving closure, the bladder was filled with normal saline to check the integrity of our closure. The saline was subsequently evacuated, and the pigs were extubated. The control group pig (n = 1) underwent the procedure except for the bladder closure and a Foley catheter being placed for 2 d postoperatively.

## RESULTS

### Postoperative Period

All 4 piglets (1 control, 3 treatment) were survived for 2 wk. Intraoperative bladder closure was not done in the control piglet and instead a Foley catheter was placed in situ for 2 d, after which it was subsequently removed. In the postoperative period, none of the piglets showed any signs of pain, distress, or decreased appetite. All of them voided normally, and the postoperative course was uneventful. After 2 wk, they were euthanized and necropsies were performed. At necropsy, gross examination of the abdominal cavity was performed, specifically looking for bowel injury, intraabdominal adhesions, abscess, and adhesions to the bladder. The bladder wall was also examined closely to examine the integrity of the repair, which was done with over distention of the dissected bladder. This was further evaluated under



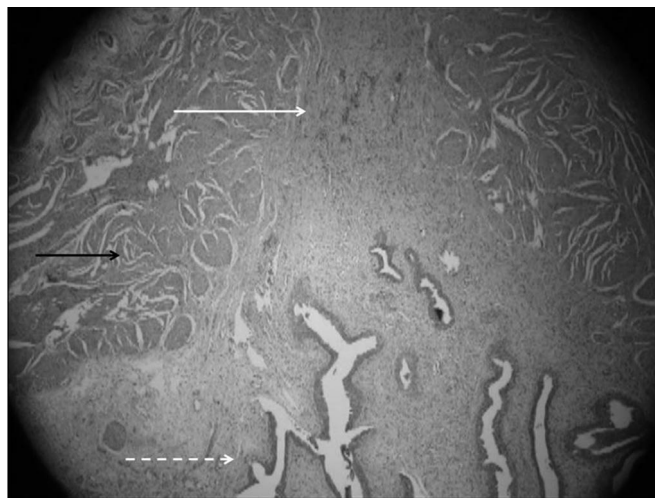
**Figure 3.** Healed bladder scar at autopsy.

the microscope by taking sections of normal bladder wall as well as the scar region and using H&E staining. The hepatic and omental biopsies were also subjected to microscopic examination to test for adequacy of the sample taken.

### Necropsy Findings

No bowel injury was noted in any of the 4 cases on gross examination. No intraabdominal adhesions or abscesses were seen and no adhesions of adjacent viscera to the bladder were observed. The bladder capacity was noted to be unaltered at 200 to 250 mL. The cystotomy incision was noted to be well healed, both grossly (**Figure 3**) and on histopathological examination (**Figure 4**). Microscopic examination of the healed bladder scar (H&E staining) revealed well-healed scar with good granulation tissue formation (**Figure 4**).





**Figure 4.** Histology of bladder scar. White marker shows healed cystotomy site. Black marker shows the bladder wall muscle fibers. Interrupted line, white marker shows bladder mucosa.

## DISCUSSION

NOTES is no longer a nascent technology, as it continues to evolve and mature at a rapid pace. Consequently, the skill set of surgeons needs to evolve alongside of it. Although endoscopists and laparoscopic surgeons already possess the skills necessary to perform minimally invasive procedures, additional training will be necessary to acquire the complementary skills needed for NOTES procedures involving a transvesical approach.<sup>1</sup>

With the advent of new working platforms, it is imperative to develop simulation models in the laboratory, where surgeons and residents alike can learn and practice in controlled environments, prior to implementing these techniques in animal models, and eventually in patients. Identification of a suitable animal model for transvesical NOTES does pose a challenge. Even though many have favored the porcine model, it is not exactly the same as the human bladder. The orientation and thickness of the porcine bladder differs from that in humans. Usefulness of cadaveric bladders is also limited by the fact that the tissue characteristics of both formalin-fixed and fresh-frozen bladders differ from live bladder tissue. Nevertheless, in the present circumstances, the porcine bladder provides a reasonably close analog to humans in terms of anatomy and tissue characteristics and, as such, continues to be used.

There have been numerous studies on NOTES and to date, these have conclusively demonstrated that both flexible and rigid instruments can be used in the setting of transvesical NOTES.<sup>1</sup> With development at a rapid pace in this field, new

instruments, working ports, and channels continue to be introduced into the market. We are also seeing the advent of multitasking platforms. The currently available instruments have shown to be competent in terms of performance of basic peritoneoscopes, organ biopsies and even relatively complex procedures like appendectomies and cholecystectomies. This is not to say that newer technology is not welcome; it can only serve to expand our arsenal and the possibilities. We are indeed entering a new and exciting era with NOTES. Intraoperative organs are visualized in a direct line of sight using transvesical access, which decreases the complexity of spatial orientation that may be encountered with access through other orifices, such as the transgastric route.

The other major concern with NOTES is that of the need to achieve and, more so, to maintain pneumoperitoneum. In our study, as with some other studies in this field, we demonstrated successful insufflations and maintenance of pneumoperitoneum through the working channel of the cystoscope. We encountered no difficulty with maintaining a seal around the scope in the transvesical approach, because the cystotomy snugly fit around the cystoscope. Therefore, we conclude that this is a feasible alternative for maintaining a pneumoperitoneum, and lends itself towards other possibilities, namely for performing both basic and, hopefully in the future, more complex abdominal surgical procedures through the transvesical approach.

The advantages of NOTES include elimination of abdominal incisions. This not only enhances cosmesis, but also decreases the potential for abdominal herniation, wound infections, postoperative ileus and pain.<sup>5</sup> As stated above, using the transvesical route, thereby eliminating the transintestinal approach, minimizes the risk of peritoneal and abdominal contamination by gastrointestinal microorganisms. McGee et al.<sup>5</sup> in their review of the evolution of NOTES, reported a 28% rate of infection-related complications in animals undergoing NOTES procedures via a transintestinal (gastric/colonic) route; 29% of these animals needed to be euthanized earlier in their respective studies due to sepsis secondary to intestinal leakage. We did not encounter any such problems due to the transvesical approach, which bodes well for this procedure.

NOTES is certainly evolving rapidly. According to the study published by Della Flora et al.<sup>2</sup> only 3 trials were registered with the Clinical Trials Register in 2008, at which time none was complete and only 1 article had been published. Now, we have reports of human transvaginal cholecystectomies being performed without complications by Bessler et al.<sup>7</sup> in New York City (Hybrid), by Zorron et al.<sup>8</sup> in Rio De Janeiro,

Brazil, and by a group led by Marescaux<sup>9</sup> in Strasbourg, France. Additionally, Swanstrom's group<sup>10</sup> in Portland, Oregon is now performing transgastric cholecystectomies, having started early and published their findings in 2007. This modality has great potential to develop as a viable alternative to conventional laparoscopic surgery.

These developments in NOTES have been recognized widely, attracting the attention of many prominent surgeons and gastroenterologists who have formed collaborations to identify concerns and challenges in the development of this technology.<sup>2</sup> A working group established at the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) leadership meeting in Chicago (2005) developed guidelines for the implementation of NOTES, which were outlined in the resulting "NOTES White Paper."<sup>11</sup> It was apparent that although performing NOTES procedures is technically possible, substantial refinement is needed in this field in terms of technology, for comparison with established procedures in a clinical setting. The aim of our study was to contribute towards this refinement, by demonstrating the efficacy of the transvesical route as a safe portal of entry into the abdominal cavity, and performing procedures thereon. We are confident that, as technology continues to develop, more complex procedures will also become possible through this approach. Further, the endoscopic bladder closure that we successfully achieved also demonstrates a viable means of closure of the access site, given that none of our test pigs developed any clinical signs of peritonitis while alive, and upon necropsy showed no observable intraperitoneal changes.

We can conclude that NOTES has blurred the boundaries between traditional endoscopy and surgery. However, we caution that NOTES is first and foremost a surgical procedure with the potential for complications, and as such should be developed and utilized only by those specialists who are able to address these potential complications, which may require conversion to traditional laparoscopic or even an open approach. More studies are required in this field, particularly in areas comparing the safety, efficacy, and complication rates of NOTES with conventional laparoscopic procedures in a controlled, randomized clinical setting.

## CONCLUSION

We have attempted to demonstrate that our approach is a safe NOTES technique, using a pure transvesical approach. This overcomes the problems with previously reported techniques, which have a risk of bowel injury. Further, using a flexible scope has the advantage of gaining optimal access to

all the intraperitoneal organs in the abdomen as well as the pelvis by virtue of the retroflex view. This, combined with flexible graspers and cautery, makes it possible to perform simple procedures like biopsies for virtually all intraabdominal organs. More complex procedures are currently limited in their scope by the technology available to us. However, this is improving at a rapid pace. In our study, we have been able to demonstrate successful biopsies with good hemostasis, and subsequent safe bladder closure.

## References:

1. Granberg CF, Frank I, Gettman MT. Transvesical NOTES: Current experience and potential implications for urologic applications. *J Endourol.* 2009;23(5):747–752.
2. Flora ED, Wilson TG, Martin IJ, O'Rourke NA, Maddern GJ. A review of natural orifice transluminal endoscopic surgery (NOTES) for intra-abdominal surgery: experimental models, techniques, and applicability to the clinical setting. *Ann Surg.* 2008;247(4):583–602.
3. Lima E, Rolanda C, Pêgo JM, et al. Transvesical endoscopic peritoneoscopy: a novel 5 mm port for intra-abdominal scarless surgery. *J Urol.* 2006;176(2):802–805.
4. Metzelder M, Vieten G, Gosemann JH, Ure B, Kuebler JF. Endoloop closure of the urinary bladder is safe and efficient in female piglets undergoing transurethral NOTES nephrectomy. *Eur J Pediatr Surg.* 2009;19(6):362–365.
5. McGee SM, Routh JC, Pereira CW, Gettman MT. Minimal contamination of the human peritoneum after transvesical incision. *J Endourol.* 2009;23(4):659–663.
6. Moran EA, Gostout CJ. Anatomical considerations for natural orifice transluminal endoscopic surgery. *Clin Anat.* 2009;22(5):627–632.
7. Bessler M, Stevens PD, Milone L, Parikh M, Fowler D. Transvaginal laparoscopically assisted endoscopic cholecystectomy: a hybrid approach to natural orifice surgery. *Gastrointest Endosc.* 2007;66(6):1243–1245.
8. Zorron R, Maggioni LC, Pombo L, Oliveira AL, Carvalho GL, Filgueiras M. NOTES transvaginal cholecystectomy: preliminary clinical application. *Surg Endosc.* 2008;22(2):542–547.
9. Marescaux J, Dallemagne B, Perretta S, Wattiez A, Mutter D, Coumaros D. Surgery without scars: report of transluminal cholecystectomy in a human being. *Arch Surg.* 2007;142(9):823–826.
10. Mellinger JD, MacFadyen BV, Kozarek RA, Soper ND, Birkett DH, Swanstrom LL. Initial experience with a novel endoscopic device allowing intragastric manipulation and plication. *Surg Endosc.* 2007;21(6):1002–1005.
11. Rattner D. Introduction to NOTES White Paper. *Surg Endosc.* 2006;20(2):185.